UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,034	03/01/2002	Francisco Javier Lopez-Tapia	R0089C-REG	6525

24372 7590 10/22/2003

ROCHE PALO ALTO LLC
PATENT LAW DEPT. M/S A2-250
3431 HILLVIEW AVENUE
PALO ALTO, CA 94304

EXAMINER	
PATEL, SUDHAKER B	

ART UNIT	PAPER NUMBER
1624	5

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,034	LOPEZ-TAPIA ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *13-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 22-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1,2* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *5* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II invention in Paper No. 4 dated 9/18/03 is acknowledged. Applicants' remarks and arguments have been considered and found persuasive. Accordingly, the restriction election is compacted as follows.

Group I (= old Group II), claims (in part) 1-12,22-38, drawn to compounds, composition, a method of use, and the first recited process of making) generic Formula I (= G1-CH2-O- Claims (in part CO-N-G2), wherein A = Aryl, G1 = Benzofuran; G2 = Non-heterocyclic, classified in class 549, subclasses various depending on the nature of variables.

Group II Claims, 1-38, drawn to compounds not included in above Groups I, classified in various classes, subclasses various depending on the nature of the variables. If this group is elected, further restriction will be required as there are many unknowns. Additionally, a single species from the working examples with all variables exactly and definitely defined must be disclosed.

2. Applicants confirmed (see enclosed interview summary) the election without traverse of above stated invention of Group I, and also the species of Example 1(= 4-(5-Phenyl-benzofuran-2-ylmethoxycarbonylamino)-biphenyl-3-carboxylic acid) as recited on page 38 of specification. Claims13-21 is withdrawn from further consideration by the examiner, as the same constitute non-elected subject matter. See 37 CFR 1.142(b).

Since claims1-12, 22-38 links with other inventions, this application will be examined bearing in mind the subject matter as elected by the applicants only.

The requirement is still deemed proper and is therefore made FINAL.

First action on merits follows.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 3/1/02 and also on 7/30/02 are being considered by the examiner. Signed copies of PTO FORM 1449 are enclosed with this communication for applicants' record.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims1-12,22-30,37,38 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A). Claims 1,37,38 recite the generic Formula as: " G1-CH2-O-CO-N-G2". The valence of N atom is incomplete. Specification also recites the same at many places. e.g. Example 1 in page 38,Example 2 in page 42, Example 5 in page 48, and Examples 6-8 in pages 51-53 respectively. Correction is required.

(B). Claim 1 recites: " A compound comprising...". Correction to: "A compound of Formula I" is required.

(C). Claim 1 recites R1 and R2 variables as:"heteroaryl optionally substituted". The claim does not exactly recite: (1). Size of the ring. (2) Number of heteroatoms in a ring.(3). Ring's connection with the main core. Therefore, it is very difficult to read the claimed invention exactly.

(D). Claims 1,38 recite the "tetrazole" core with 1 N atom having unsatisfied valence. The same is the situation in the specification. E.g. Example 5 in page 48. Correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 31-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for asthma, does not reasonably provide enablement for treating a subject with a disease state that is alleviated with an IP antagonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Specification in pages 1-3 recite involvement of prostaglandins in pathophysiology of bladder disorders, platelets and blood vessels, antithrombogenic properties of the intact vascular wall, prevention of conditions associated with excessive bleeding, induction of hyperalgesia, inflammation and pain, respiratory allergies and other conditions yet to be discovered.

8. In cases directed to chemical compounds, which are being used for their physiological/biological activity, the scope of the claims must have a reasonable

correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.

9. "Isomers, mixtures of racemates, Solvates and pharmaceutically acceptable Salts" as recited in the claims read on all such moieties regardless of complexity of structure and point of attachment to the aliphatic or carbocyclic or aromatic or heterocyclic core or bridge/chain for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a compound of claim 1(or claims dependent on it) and/ or its composition in its "Isomers, mixtures of racemates, Solvates and pharmaceutically acceptable Salts' form". Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their combinations either alone or in a combination as outlined, will have ability to generate the compounds in vivo or in vitro by one or more processes.

10. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:***(1).*** The nature of invention;***(2).*** the state of prior art ;***(3).*** the predictability or lack thereof in the art;***(4).*** the amount of direction or guidance present;***(5).*** the presence or absence of working examples;***(6).*** the breadth of the claims, and ***(7).*** the quantity of experimentation needed.

- **Discussion about inflammation:**

Enablement for the scope of "inflammatory diseases" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process, which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages, which have stuck tightly together,

typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulites is inflammation of the tissues around eye, and Orbital cellulites is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Discussion about non-steroidal anti-inflammatory agents:

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications(Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of the causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Following references are cited to show the state of art for inflammation:

- **Status of current understanding about nonsteroidal anti-inflammatory drugs:**

Liu et al(PubMed Abstract 12447698, also cited as Oncogene, 21/54,8347-50(2002)). States that: " NSAIDs are known to exert anti-angiogenic and anti-metastatic activity both in vitro and in vivo..... We also found that NSAID-activated RECK expression might not be mediated via inhibition of COXs..Taken together, our results suggest that induction of **RECK expression may be one of the mechanisms** by which NSAIDs suppress MMP activity to block angiogenesis and metastasis".

- **Involvement of different PGs in inflammatory reaction(s):**

Ueno et al(PubMed Abstract 113383 74, also cited as Nippon Yakurigaku Zasshi, 117/4,255-61(2001)). State that:" However, in the LPS-pretreated mice, not only PGI2 but also other PGs produced by COX-2 may be involved in pain induction. Production of TNF alpha and IL-10 was modified with PGI2 or PGE2; the production of TNF alpha

was doen-regulated by the stimulation via IP-, EP2- or EP4 receptor, but that of IL-10 was up-regulated by these receptors, resulting in an anti-anti-inflammatory effect".

- **Need for analgesics with fewer side effects:**

Kuraishi et al (PubMed Abstract 11338373, also cited as Nippon Yakurigaku Zasshi, 117/4,248-54(2001)) state that: " The determination of precise roles of prostanoids in pain and fever may provide new targets for antipyretic analgesics with fewer side effects ".

- **Effect of available benzofuran derivative (= TRK-100) in the dog:**

Nishio et al(PubMed Abstract 2514128, also cited as Nippon Yakurigaku Zasshi, 94/6,351-61(1989)) state that:" The effect was similar to PGI2. Coronary vascular resistance, total peripheral resistance and systemic blood pressure were also decreased by TRK-100 and PGI2".

- **Prostaglandins;their biological and pharmaceutical role:**

Vapaatalo et al (PubMed Abstract 212650, also cited as Med. Biol., 56/4,163-83(1978)) state that:' Although the field is generally promising, there are many contradictory findings. This calls for a cautious interpretation of the many interesting observations".

Specification on pages 27, 58-63 recites various tests and assay methods for activity related to IP receptor. .

Applicants have not provided specific results for the activities recited herein. e.g. Test results for Experiment 16 are concluded in page 59, line 1 as:" Compounds of the invention were active in this assay". Similar conclusions are recited in page 59, line 30

for Example 17,in page 60, line 28 for Example 18, and also for Examples 19-21. Therefore, comparison among the compounds can not be made with the art-recognized ref. Compounds for different assays.

Such results and assays will only serve for the preliminary screening of many compounds, and not for treating the diseases or conditions as claimed herein.

The facts as provided above do support the need for additional quantity of experimentation, which would be an undue burden to one skilled in the pharmaceutical arts, since there is inadequate guidance given to the skilled artisan, regarding the method of treatment for various disorders/conditions related to inflammation as well as other pathophysiology.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of instant compounds to control or prevent disorders related to inflammation

When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Conclusion

Allowable Subject Matter

11. The following is a statement of reasons for the indication of allowable subject matter: The closest prior art of record reference Suzuki et al (EP 974576) teaches

method of producing benzamde derivatives. See abstract, compound 9 in page 5, Compounds 17-1 to 17-3 in page 9, and claims 1-29 in pages 23-30.

12. The reference '576 differs from the instant claims by not having a tetrazole ring connected to phenyl ring by a –CH2- bridge, but by a diazole ring connected to phenyl ring by a –CO-bridge.

13. The reference '576 does not indicate or suggest to arrive at the instant claims having a core:" Phenyl-Benzofuran-CH2-O-CO-NH-Aryl-(CH2)n-COOH/Tetrazole".

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is 703 308 4709. The examiner can normally be reached on 6:30 to 5:00 pm. Monday-Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on 703 308 4716 or Sr. Examiner Mr. Richard Raymond at 703 308 4523.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.

JOHN M. FORD
PRIMARY EXAMINER
GROUP - ART UNIT 1624

Sudhaker B. Patel, D.Sc.Tech.
October 15, 2003.